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STN Search

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L1 15252 (ORAL OR MOUTH OR SUBLINGUAL) (S) (VACCINE OR IMMUN?) AND (MUCOS ##### OR MUCOUS?)

L7 51 L6 AND (TONGUE OR SUBLINGUAL OR SUB-LINGUAL OR (FLOOR OR BASE) (S) MOUTH)

L9 5430 L2 AND (VACCINE OR IMMUN?) (5N) (MUCOS##### OR MUCOUS? OR BUCCAL OR ORAL OR TONGUE OR SUBLINGUAL OR SUB-LINGUAL)

L14 0 L13 AND (TONGUE OR SUBLINGUAL OR SUB-LINGUAL OR (FLOOR OR BASE)(S) MOUTH)

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FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 10:11:46 ON 03 DEC 2004

L1 15252 S (ORAL OR MOUTH OR SUBLINGUAL) (S) (VACCINE OR IMMUN?) AND (MU
L2 8758 S L1 AND (HUMAN OR HIV## OR MONKEY OR PRIMATE)
L3 6976 S L2 AND (VACCINE OR IMMUN?) (S) (MUCOS##### OR MUCOUS?)
L4 1262 S L2 AND (HIV OR HUMAN (A) IMMUNODEF? (A) VIRUS)
L5 1009 S L3 AND L4
L6 508 S L5 AND PY<1999
L7 51 S L6 AND (TONGUE OR SUBLINGUAL OR SUB-LINGUAL OR (FLOOR OR BAS
L8 30 DUP REM L7 (21 DUPLICATES REMOVED)
L9 5430 S L2 AND (VACCINE OR IMMUN?) (5N) (MUCOS##### OR MUCOUS? OR BU
L10 321 S L9 AND L6
L11 160 DUP REM L10 (161 DUPLICATES REMOVED)
L12 0 S L11 NOT L6
L13 147 S L11 NOT L7
L14 0 S L13 AND (TONGUE OR SUBLINGUAL OR SUB-LINGUAL OR (FLOOR OR BAS
L15 53 S L13 AND (MUCOUS#### OR MUCOS######)/TI
L16 3433 S L1 AND ((ORAL OR SUBLINGUAL) (S) IMMUN?)/TI
L17 336 S L16 AND L4
L18 51 S L7 AND PY<1999
L19 21 S L18 NOT (L15 OR L8)
L20 11 DUP REM L19 (10 DUPLICATES REMOVED)

L8 ANSWER 6 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:449824 CAPLUS
DN 125:78563
TI Delivery of expression vectors for antigen genes to **mucosal** tissue and their use in the induction of **mucosal immunity**
IN Weiner, David B.; Wang, Bin; Ugen, Kenneth E.
PA Trustees of the University of Pennsylvania, USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9618390	A1	19960620	WO 1995-US16206	19951215 <--
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6348449	B1	20020219	US 1994-357398	19941216
	AU 9645169	A1	19960703	AU 1996-45169	19951215 <--
	AU 701208	B2	19990121		
	EP 796104	A1	19970924	EP 1995-943781	19951215 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
PRAI	US 1994-357398	A	19941216		
	US 1993-125012	A2	19930921		
	WO 1995-US16206	W	19951215		

AB Methods of introducing genetic material into cells of an individual, specifically expression cassettes encoding protective antigens and capable of inducing **mucosal immunity** are described. The nucleic acids are administered topically or by lavage into **mucosal** tissue (rectal, vaginal, urethral, **sublingual** or buccal). Individuals may be immunized against a pathogen, hyperproliferative or autoimmune diseases. A series of expression vectors for antigens of **HIV**-1 are described. Mice inoculated vaginally with a plasmid carrying a β-galactosidase reporter gene under control of a cytomegalovirus promoter showed rapid spread and persistent expression of the β-galactosidase gene throughout **mucosal** and non-**mucosal** tissue. Inoculation with a similar plasmid carrying the **HIV**-1 env gene led to a strong IgA response that persisted for at least 180 days.

BF23, which used *btuB* as a cell surface receptor to gain entry into *E. coli*. Because *birA* is an essential gene, recombinants at *birA* were screened by electron microscopy.
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15. Sample size (*n*) for measurements of different features in a given replication time period varied because debris or tangled strands often prevented measurement of all features on every micrograph.
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26. I thank N. Panayotatos for plasmid pLA512, R. Kadner for pAG1, A. Campbell for pAB11, M. Sikes for carbon-coated microscope grids, and O. L. Miller, Jr., for the opportunity to work in his laboratory where these experiments were conducted. I also thank A. Beyer, R. Kadner, and Y. Osheim for helpful comments on the manuscript. Supported by PHS grant GM 21020 from the NIH.

15 June 1992; accepted 1 September 1992

Induction of Mucosal and Systemic Immunity to a Recombinant Simian Immunodeficiency Viral Protein

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Heterosexual transmission through the cervico-vaginal mucosa is the principal route of human immunodeficiency virus (HIV) infection in Africa and is increasing in the United States and Europe. Vaginal immunization with simian immunodeficiency virus (SIV) had not yet been studied in nonhuman primates. Immune responses in macaques were investigated by stimulation of the genital and gut-associated lymphoid tissue with a recombinant, particulate SIV antigen. Vaginal, followed by oral, administration of the vaccine elicited three types of immunity: (i) gag protein p27–specific, secretory immunoglobulin A (IgA) and immunoglobulin G (IgG) in the vaginal fluid, (ii) specific CD4$^+$ T cell proliferation and helper function in B cell p27-specific IgA synthesis in the genital lymph nodes, and (iii) specific serum IgA and IgG, with CD4$^+$ T cell proliferative and helper functions in the circulating blood.

Vaginal transmission of SIV has been achieved experimentally in macaques, resulting in the development of an acquired immunodeficiency syndrome (AIDS)–like syndrome (*1*). This route of infection resembles heterosexual transmission of HIV in humans. Although systemic immunization strategies have protected against intravenous challenges with infectious SIV (*2*), they have not prevented vaginal transmission (*1*). In view of these observations and the prevalence of heterosexual transmission of HIV in humans, the development of a simian model of vaccination that can prevent genital transmission of SIV has been emphasized (*3*).

We have shown that protein p1, encoded by the yeast retrotransposon Ty, can be used as a carrier for recombinant antigens and that p1 fusion proteins self-assemble into hybrid virus-like particles (Ty-VLP) (*4*). Systemic immunization studies demonstrated that hybrid particles that carry the SIV gag protein p27 (SIV p27:Ty-VLP) induce both circulating antibody and T cell responses in macaques (*4*). Administration of SIVmac$_{251}$ whole, inactivated vaccine or synthetic peptides by the mucosal route did not induce an effective immune response (*5*). We therefore attempted to use SIV p27:Ty-VLP to stimulate the mucosal-associated lymphoid tissue (*6*). The SIV p27:Ty-VLP was conjugated to the GM1 ganglioside receptor–binding subunit of cholera toxin (CTB), which has potent mucosal adjuvant properties (*7*). We used two separate immunization regimes to assess the p27:Ty-VLP/CTB vaccine that was administered by nontraumatic vaginal and oral instillation. Three macaques received two oral, followed by three vaginal, administrations (O-V), and four macaques received two vaginal, followed by three oral, administrations (V-O) of the vaccine. Four macaques were used as controls by administration of p27:Ty-VLP without CTB, p27 conjugated to CTB (p27/CTB), or p27 alone, all by the O-V route to one macaque each, or by administration of Ty-VLPs conjugated to CTB (Ty-VLP/CTB) by the V-O route to one macaque.

Sequential examination of vaginal, rectal, salivary, and serum antibodies before and after each of the oral and vaginal immunizations with p27:Ty-VLP/CTB showed that IgA (Fig. 1 and Table 1) and IgG (Fig. 2 and Table 1) were specifically raised to p27 (anti-p27). IgA and IgG anti-p27 in vaginal fluid were found after the first or second oral or vaginal immunization in one macaque in each group. In the other macaques immunized by the O-V route, antibodies increased after the fifth mucosal immunization. The macaques in the second group immunized by the V-O route showed an increase in antibodies after the fourth or fifth mucosal immunization. Similar results were found with serum IgA and IgG, except that these were detected earlier (Figs. 1 and 2). Salivary IgA, but not IgG, appeared early, after the first or second vaginal immunization in the V-O group and to a lesser extent in the O-V group (Table 1). Rectal washings showed anti-p27 IgA in only three out of seven macaques and IgG in one out of seven macaques after the fifth mucosal immunization. Of the four control macaques, those immunized with p27:Ty-VLP, p27 alone, or Ty-VLP/CTB did not show IgA or IgG in vaginal and rectal fluids, whereas p27/CTB elicited some antibodies in vaginal fluid (Figs. 1 and 2). However, all but Ty-VLP elicited serum IgA and IgG anti-p27. Immunization with p27/CTB or p27 also induced salivary IgA and IgG (Table 1). One-way analysis of variance (ANOVA) of vaginal anti-p27 IgA in macaques immunized with p27:Ty-VLP/CTB by the V-O route, as compared with the control group, showed a significant difference (P = 0.017), and anti-p27 IgG was also significant (P = 0.022). Although vaginal IgA elicited by the O-V sequence of immunization was significant (P = 0.025), IgG (P = 0.44) did not reach the 5% level of significance. By either sequence of immunization, serum anti-p27 IgA was not significant if the immunized group was compared with the control group (P = 0.057 and 0.143) because among the control macaques all but Ty-VLP/CTB elicited serum IgA (Figs. 1 and 2). However, serum

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IgG by the O-V route reached a significant difference ($P = 0.006$) but not by the V-O sequence ($P = 0.056$).

After the final mucosal immunization, the macaques were immunized by the intramuscular (IM) route with the vaccine used for mucosal immunization. Increases in vaginal, serum, and salivary IgA and IgG were recorded in three out of four macaques immunized by the V-O route. However, O-V immunization resulted in an increase of vaginal IgA in two out of three animals but not in IgG. No increases were seen in serum or salivary IgA and IgG after O-V immunization; salivary, and to a lesser extent, vaginal and serum antibodies actually decreased in some macaques (Figs. 1 and 2 and Table 1). IM challenge did not increase rectal antibody titers. One-way ANOVA of the V-O sequence followed by IM immunization showed a significant increase in IgA ($P = 0.027$) and IgG ($P = 0.008$) when the titers after the three oral immunizations were compared with that of the IM immunization; significant results were not found with the O-V sequence of immunization ($P > 0.2$).

The sensitivity of the enzyme-linked immunosorbent assay (ELISA) method was determined by means of affinity-purified anti-p27 IgA and IgG (8). These antibodies were used in an ELISA and showed that the sensitivity for anti-p27 IgA reached 59 ng/ml and that for IgG it was 18 ng/ml. A comparison of serum with vaginal antibodies revealed that representative serum anti-p27 IgA was 168.4 μg/ml and that for IgG it was 62.1 μg/ml, whereas in vaginal washings anti-p27 IgA was 490 ng/ml and IgG was 60 ng/ml. In addition, vaginal IgA is underestimated by a factor of about 3 because we used monomeric serum IgA standard to estimate polymeric IgA. Furthermore, both vaginal IgA and IgG antibodies are greatly underestimated because washings were used, which introduces an unknown dilution factor.

The specificity of anti-p27 was demonstrated by the fact that antibodies were not raised in the vaginal washings, sera, or saliva to a random peptide or to Ty-VLP after mucosal immunization. Furthermore, adsorption of vaginal fluid, serum, or saliva by Sepharose beads coated with p27 abrogated IgA and IgG titers, unlike beads coated with control tetanus toxoid (TT) antigen that had little effect on the antibody titers (9). The vaginal IgA was of the polymeric secretory type, as demonstrated by ELISA with a goat antibody to human IgA secretory component and a goat antibody to human IgA J chain. Thus, anti-p27 in vaginal fluid detected by antibodies to IgA secretory component or J chain yielded titers of 1:8 to 1:16. In contrast, serum anti-p27 IgA in the same macaque revealed a titer of 1:1600 with antibody to IgA but only 1:100 with antibody to secretory component. To examine for J chains, the serum IgA had to be separated from IgM (which also has J chains), and the pure IgA showed an anti-p27 titer of 1:128 with the antibody to IgA but only 1:2 with the antibody to J chain.

The detection of p27-specific antibodies in the serum of macaques immunized through the mucosa suggested that IgA- and IgG-producing B cells migrated from the mucosal-associated lymphoid tissues into the circulation (6). These cells could then recirculate and go to other mucosal-associated

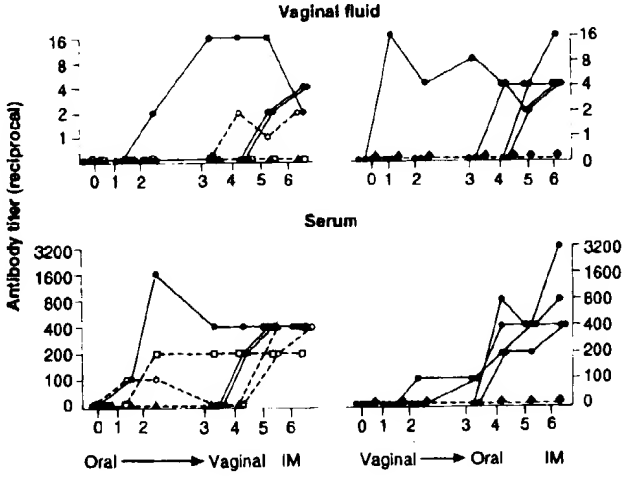

Fig. 1. IgA anti-p27 in vaginal fluid or serum were determined by ELISA after O-V or V-O immunization of macaques with SIV p27:Ty-VLP/CTB (●, solid lines), p27:Ty-VLP (□, dotted lines), p27/CTB (○, dotted lines), p27 (▲, dotted lines), or Ty-VLP/CTB (◆, dotted lines) (*16, 17*).

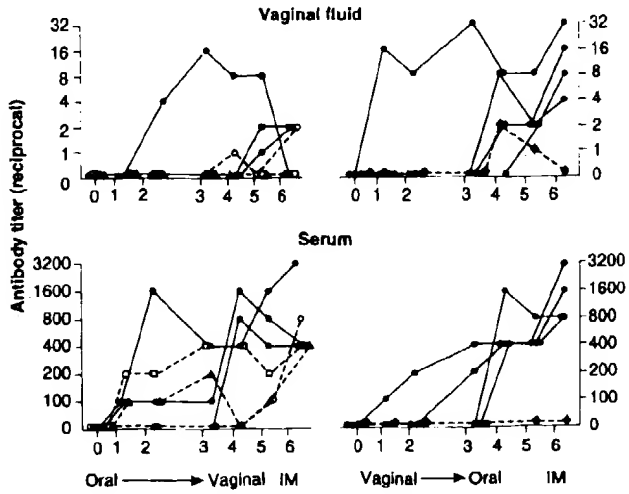

Fig. 2. IgG anti-p27 in vaginal fluid or serum after O-V or V-O immunization of macaques with SIV p27:Ty-VLP/CTB (●, solid lines), p27:Ty-VLP (□, dotted lines), p27/CTB (○, dotted lines), p27 (▲, dotted lines), or Ty-VLP/CTB (◆, dotted lines). The methods used were as described (*16, 17*), except that IgG anti-p27 was detected with a rabbit IgG to monkey IgG (2 μg/ml; Nordic Immunological Laboratory).

Table 1. Salivary IgA and IgG anti-p27 antibodies were determined by ELISA (*16*). Saliva was collected in petri dishes after pilocarpine stimulation. The results are expressed as reciprocal titers of the lowest dilution that gives an absorbance of 0.15 units above the background sample. PI, before immunization; ND, not determined.

Vaccine	PI	Immunizations					
		1	2	3	4	5	6
	IgA anti-p27						
		Oral			Vaginal		IM
p27:Ty-VLP/CTB	0	2	1	0	32	8	8
p27:Ty-VLP/CTB	0	0	16	0	0	8	0
p27:Ty-VLP/CTB	0	2	0	0	0	8	8
p27:Ty-VLP	0	0	0	0	0	0	ND
p27-CTB	0	32	8	8	16	4	2
p27	0	16	8	0	1	16	16
		Vaginal			Oral		IM
p27:Ty-VLP/CTB	0	8	4	2	16	4	4
p27:Ty-VLP/CTB	0	0	2	2	16	2	16
p27:Ty-VLP/CTB	0	8	4	0	2	2	4
p27:Ty-VLP/CTB	0	0	0	0	0	0	4
Ty-VLP/CTB	0	0	0	0	0	0	0
	IgG anti-p27						
		Oral			Vaginal		IM
p27:Ty-VLP/CTB	0	0	0	0	32	2	4
p27:Ty-VLP/CTB	0	0	0	0	0	8	8
p27:Ty-VLP/CTB	0	0	0	0	0	4	2
p27:Ty-VLP	0	0	0	0	0	0	ND
p27-CTB	0	0	0	2	2	1	0
p27	0	4	0	0	0	8	16
		Vaginal			Oral		IM
p27:Ty-VLP/CTB	0	0	0	0	0	0	0
p27:Ty-VLP/CTB	0	0	0	0	4	2	8
p27:Ty-VLP/CTB	0	0	2	0	2	0	4
p27:Ty-VLP/CTB	0	0	0	0	0	2	4
Ty-VLP	0	0	0	0	0	0	0

lymphoid tissues to produce antibodies (for example, in saliva) after vaginal and oral immunization. These observations are consistent with other studies, mostly in rodents, in which oral immunization with a variety of antigens (but not HIV or SIV) induced antibodies in the genital tract (*10*) and cervico-vaginal or uterine immunization (*11*) resulted in the production of local and, in some cases, systemic antibodies. The induction of systemic antibodies after mucosal immunization with p27:Ty-VLP/CTB led us to investigate whether p27-sensitized T cells could be detected in the circulation.

Peripheral blood lymphocytes from the immunized animals were stimulated in vitro with p27, and the uptake of ^{3}H-labeled thymidine was recorded both in absolute counts per minute and as stimulation indices (Fig. 3). Specific proliferation of lymphocytes stimulated with p27 (but not with Ty-VLP/CTB alone or the control peptide) was detected earlier than the corresponding antibodies. In two of the three macaques in the O-V group, the stimulation index was >2 after the first oral immunization; the third macaque showed a specific increase in the lymphoproliferative response only after the first vaginal immunization. In the V-O group, two out of four macaques showed a significant stimulation index after vaginal immunization, with the remaining two macaques converting after subsequent oral immunizations. The lymphoproliferative responses were augmented in all four macaques after oral immunization of the V-O group of animals. Expression of the results of [^{3}H]thymidine uptake also showed an increase in counts per minute in all macaques after vaginal immunization (in the V-O group) or oral immunization (in the O-V group) with gag p27:Ty-VLP/CTB. However, V-O immunization yielded higher stimulation indices after the last mucosal immunization (7.6, 7.0, 5.1, and 2.4) than those after O-V immunization (6.2, 3.0, and 2.6). One-way ANOVA of the stimulation indices of either the V-O or O-V sequence of immunization, as compared with those of the controls, showed a significant difference ($P < 0.0001$).

IM challenge after mucosal immunization elicited a significant increase in T cell p27 stimulation indices in vitro in three out of four macaques immunized by the V-O route (net increases of 7.5, 7.4, and 5.0; $P = 0.01$), as compared with lower and insignificant increases in the O-V immunized group (5.0, 2.8, and 2.8; $P = 0.077$) (Fig. 3). The four control macaques immunized with p27:Ty-VLP, p27/CTB, p27, or Ty-VLP/CTB did not induce significant lymphoproliferative responses to p27 (Fig. 3). To determine which T cell subset mediated the observed proliferative responses, we separated the T lymphocytes from four macaques into CD4- and CD8-enriched populations by panning with a monoclonal antibody to CD4 (*12*). Stimulation of these T cell subsets in vitro with p27 showed that the

Table 2. We determined in vitro IgA and IgG synthesis by reconstituting B cells, CD4$^+$ cells, macrophages, and antigen (*14*). The results are given as mean (± SEM in parentheses) of absorbance with peripheral blood cells after V-O immunization of three macaques with p27:Ty-VLP/CTB (Exp. 1), the same animals after IM immunization with p27:Ty-VLP in AluGel (Exp. 2), and a macaque immunized only by the IM route with the latter vaccine (Exp. 3). The results are presented for the genital lymph node cells and for splenic cells removed from three macaques immunized by the V-O route and boosted by IM immunization by the vaccines used in Exps. 1 and 2, respectively.

Exp.	Immunization	p27		Ty-VLP		TT	
		IgA	IgG	IgA	IgG	IgA	IgG
		Peripheral blood mononuclear cells					
1	V-O	0.218 (0.025)	0.102 (0.014)	0.081 (0.011)	0.075 (0.014)	0	0
2	V-O + IM	0.044 (0.007)	0.163 (0.024)	0.111 (0.028)	0.100 (0.037)	0	0
3	IM	0.056	0.357	0.076	0.10	0.242	0.396
		Genital lymph node cells					
4	V-O + IM	0.304 (0.031)	0.188 (0.003)	0.162	0.180	0.161 (0)	0.172 (0.01)
		Spleen cells					
5	V-O + IM	0.201 (0.023)	0.395 (0.003)	0.131	0.195	0.161 (0)	0.175 (0.013)

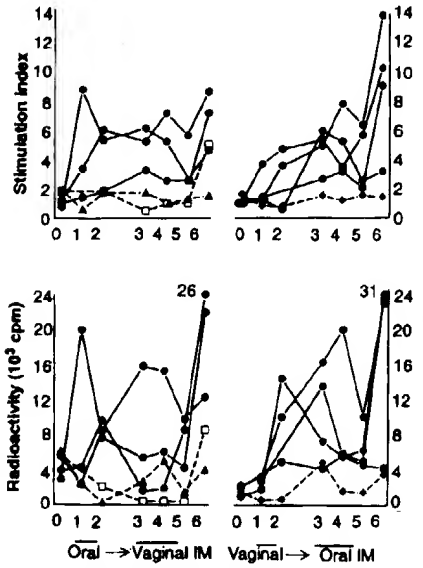

Fig. 3. The p27-specific proliferation of peripheral blood lymphocytes after O-V or V-O immunization of macaques with SIV p27:Ty-VLP/CTB (●, solid lines), p27:Ty-VLP (□, dotted lines), p27/CTB (○, dotted lines), p27 (▲, dotted lines), or Ty-VLP/CTB (◆, dotted lines) (*15*).

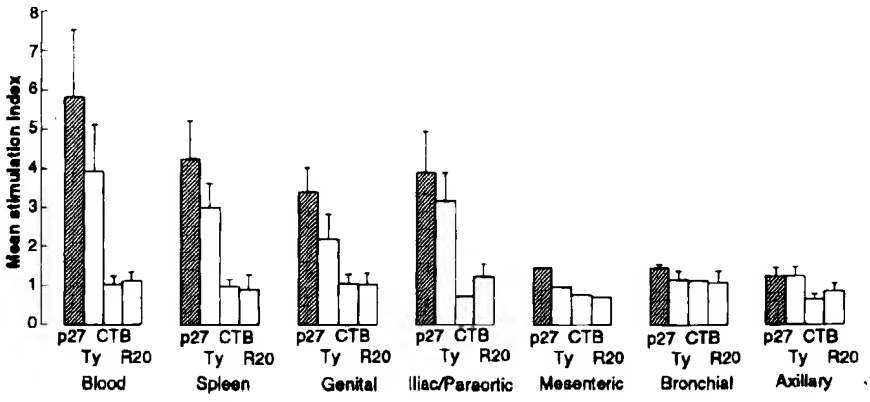

Fig. 4. The spleen, genital (obturator), iliac, paraortic, superior mesenteric, bronchial, and axillary lymph nodes were removed at autopsy from four macaques immunized by the V-O ($n = 2$) or O-V ($n = 2$) route and boosted by IM immunization (*12*). The cells were separated and processed after breaking up the tissues (*15*). The cells were cultured without antigen and with p27, Ty-VLP, CTB, or R20 (1, 10, and 20 μg/ml) for 5 days; only the optimal responses are presented. Because the proliferative responses of lymphocytes from the macaques immunized by the V-O route showed little difference from those immunized by the O-V route, the results are expressed as the mean stimulation index (± SEM) of the lymphoid cells of four macaques; for mesenteric lymph node cells only two macaques were examined.

responding cells belonged to the $CD4^+$ subset, which yielded a mean stimulation index of 5.4 ± 1.3 (or 7450 ± 3100 cpm), as compared with the $CD8^+$ subset, which yielded a mean stimulation index of 1.8 ± 0.2 (or 1200 ± 400 cpm).

We killed four macaques (*13*) immunized by the O-V ($n = 2$) or V-O ($n = 2$) route and removed the related and unrelated lymph nodes and spleens. Mononuclear cells isolated from the draining lymph nodes (genital, iliac, and paraortic) showed significant proliferative responses to p27 or Ty-VLP (but not to CTB or the random peptide R20) (Fig. 4). However, superior mesenteric, bronchial, or axillary lymph node cells did not respond to these antigens, although they were readily stimulated with concanavalin A. This suggests that augmented vaginal immunization does not involve the entire mucosal-associated lymphoid tissue because neither the mesenteric nor bronchial lymph nodes yielded specific lymphoproliferative responses. However, spleen cells and circulating blood cells showed significant T cell responses, indicating that vaginal immunization augmented by oral immunization elicits genital and systemic lymphoproliferative responses that are not found with the gut-associated lymphoid tissue (mesenteric) or the unstimulated bronchial-associated lymphoid tissue. We have also shown that the T cell responses involve predominantly $CD4^+$ and not $CD8^+$ cells (*12*).

To establish that mucosal immunization elicits $CD4^+$ cells in the circulation that are capable of helping B cell antibody synthesis, we carried out in vitro reconstitution experiments (*14*). Adding enriched circulating $CD4^+$ cells to B cells and macrophages from the V-O–immunized macaques and stimulation with p27 elicited specific anti-p27 IgA (Table 2, Exp. 1). However, when these macaques were challenged by the IM route, anti-p27 IgG was synthesized (Table 2, Exp. 2). Systemic immunization alone induced IgG but not IgA anti-p27, although the animal was capable of producing IgA antibodies to TT (Table 2, Exp. 3). A series of controls without one of the cells ($CD4^+$ cells, B cells, or macrophages), without antigen, or stimulation with unrelated antigen TT did not elicit anti-p27 IgA or IgG.

The results are consistent with the concept that V-O or O-V immunization activates the mucosal-associated lymphoid tissue to produce IgA, whereas IM immunization favors the IgG class of antibodies. We verified this hypothesis by comparing the isotypes of antibodies synthesized by the genital lymph node B cells, $CD4^+$ cells, and macrophages with those from the corresponding spleens in three macaques immunized by the V-O route and boosted by IM immunization (Table 2). Genital lymph node cells yielded higher anti-p27 IgA levels than for IgG (Table 2, Exp. 4), whereas higher IgG levels than for IgA were found with splenic cells (Table 2, Exp. 5). This was not found with Ty-VLP or the unrelated TT, which stimulated similar readings for both IgA and IgG. The specificity of the in vitro antibody synthesis was established because stimulation with p27 induced only anti-p27, stimulation with Ty-VLP induced only antibodies to Ty-VLP, and stimulation with TT induced only antibodies to TT. Furthermore, these experiments suggest that the $CD4^+$ cells function as helper T cells in antibody synthesis and that mucosal immunization generates both p27-sensitized $CD4^+$ cells and predominantly IgA-producing B cells in the genital lymph nodes, from which they enter the circulation. However, homing of T cells to the genital tract or the cytotoxic potential of these cells has not been explored.

Vaginal transmission of SIV might be prevented by local mucosal IgA and IgG. However, if the mucosal immune barrier were breached, a second line of defense, the genital lymph node T and B cell functions, might prevent infection. A failure of both the mucosal and genital lymph node barriers still leaves the circulating antibodies and T cells against SIV to prevent infection and the development of AIDS. We have shown that the V-O immunization regime with p27:Ty-VLP/CTB generates surface mucosal, genital lymphoid tissue, and systemic immunity, as assessed by IgA and IgG, $CD4^+$ proliferation, and helper cell function in specific antibody synthesis. This mucosal model can now be used to evaluate the ability of candidate vaccines to prevent vaginal transmission of SIV. Augmented V-O immunization strategies might also be applicable to other sexually transmitted diseases.

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7. J. Holmgren, *Nature* **292**, 413 (1981); N. Lycke and J. Holmgren, *Immunology* **59**, 301 (1986); C. O. Elson and W. Ealding, *J. Immunol.* **133**, 2892 (1984).
8. IgG was separated from serum by ion-exchange chromatography on a DEAE-cellulose column (Whatman, Maidstone, U.K.) in 0.01 M tris phosphate (pH 7.0). Partially purified IgG was adsorbed with goat antibody to IgA (Nordic Immunological Laboratory, Maidenhead, U.K.), attached to cyanogen bromide (CNBr)–activated Sepharose 4B beads (Kabi-Pharmacia, Milton Keynes, U.K.). The IgG was then affinity-purified on CNBr-activated 4B beads to which SIV p27 had been coupled. Specific monkey anti-SIV p27 IgG was eluted with 6 M guanidine hydrochloride, brought to neutrality with 2 M tris, and dialyzed against phosphate-buffered saline before assay by ELISA. IgA was separated from serum by gel filtration chromatography on a Sephadex G-200 column (Kabi-Pharmacia) in 0.1 M tris-HCl with 1 M NaCl (pH 8.0). The 7*S* peak was further chromatographed on a DEAE column as in the case of IgG. After elution of the IgG main peak, IgA was eluted by application of a salt-pH gradient of 0.01 M tris-phosphate (pH 7.0) to 0.3 M tris-phosphate (pH 4.0). We applied IgA to an affinity column of goat antibody to human IgG coupled to Sepharose 4B to remove traces of IgG. Purified IgA was then applied to a Sepharose 4B column with bound p27 and eluted as for the specific anti-p27 IgG. The concentrations of the affinity-purified anti-p27 IgA and IgG were determined by radial immunodiffusion with reference to purified rhesus monkey serum IgA and IgG standards.
9. We tested the specificity of the antibody assay by coupling p27 or TT (at 0.25, 0.5, 1, 2, and 4 μg/ml) to CNBr-activated Sepharose 4B beads. Dilutions of vaginal washings, serum, or saliva samples were incubated with the appropriate volume of beads (1 hour at 37°C and 16 hours at 4°C). The beads were centrifuged, and the adsorbed samples were tested by ELISA. All three test fluids showed complete inhibition of anti-p27 with p27 (at 2 to 4 μg/ml) but negligible inhibition with TT.
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12. Mononuclear cells were separated from defibrinated blood by Lymphoprep (Nycomed, Oslo, Norway) and density-gradient centrifugation, following the manufacturer's instructions. We isolated enriched monocytes by incubating the cells in plastic plates in RPMI 1640 medium (with 10% fetal bovine serum) for 1 hour at 37°C with 5% CO_2. Nonadherent cells were removed, and adherent cells were incubated with RPMI-1640 medium overnight at 37°C and recovered by washing the plate. The nonadherent cells were separated by established procedures on the basis of whether they bound 2-aminoethylisothiouronium (AET)–treated sheep red blood cells (T^+ cells) or did not (T^-; enriched B cells). The T cells were further separated by panning 5×10^6 cells with an optimal amount of monoclonal anti-T4 culture supernatant (100 μl per 10^6 cells) in Hanks' solution (with 10% fetal bovine serum) overnight at 4°C. After washing, 15×10^6 cells were added to petri dishes that had been coated with affinity-purified goat antibody to mouse IgG (at 5 μg/ml in 0.5 M tris-HCl, pH 9.5) for 70 min at 4°C. The nonadherent cells consisted of enriched $CD8^+$ cells, and the adherent cells were enriched $CD4^+$ cells. These enriched T cell subsets were stimulated with p27 and processed as described (*15*).
13. The macaques were killed by injection of IM ketamine hydrochloride (10 mg per kilogram of body mass; Parke-Davis Veterinary, Ponty Poole, U.K., followed by IM Rompun xylazine (20 mg/kg; Bayer Pharmaceuticals, Newbury, U.K.), and finally intravenous pentobarbitone sodium (200 mg/kg; Bayer Pharmaceuticals).
14. R. Fellowes and T. Lehner, *J. Immunol. Methods* **132**, 165 (1990). Mononuclear cells were separated from peripheral blood (*12*), and enriched B cells (10^5), $CD4^+$ cells (4×10^5), and monocytes (5×10^4) were reconstituted and stimulated with

p27, Ty-VLP, or TT (200 or 20 μg/ml) for 7 days, followed by culture without antigen for 8 days. The culture supernatants were assayed for the corresponding IgA or IgG by a modified ELISA. Microtiter plates were coated with antigen (p27, p27:Ty-VLP, Ty-VLP, or TT; 1 μg/ml). Culture supernatants were diluted 1:1 with RPMI 1640 medium before incubation. Bound antibody was detected with goat antibody to monkey IgA or IgG (Nordic Immunological Laboratory), followed by biotinylated rabbit antibody to goat IgG, horseradish peroxidase, and phenylenediamine dihydrochloride. The reaction was terminated with 2 M H_2SO_4. The results are expressed as mean (± SEM) absorbance at a wavelength of 492 nm, with the absorbance of the control culture (of $CD4^+$ cells, B cells, and macrophages but without antigen) subtracted. The results are presented only for stimulation with p27 (200 ng/ml), Ty-VLP (200 ng/ml), or TT (20 ng/ml) and tested against the corresponding antigen. Stimulation with one antigen and tested against another antigen did not show an absorbance greater than 0.15 unit. A control macaque immunized by the V-O route with Ty-VLP/CTB and boosted by IM immunization did not yield anti-p27.

15. Mononuclear cells were separated (*12*) and cultured without antigen and with p27, p27:Ty-VLP, Ty-VLP, CTB, R20, and concanavalin A (1, 10, and 20 μg/ml) in 96-well round-bottomed plates (Costar) containing RPMI 1640 medium (Gibco) supplemented with penicillin (100 units/ml; Sigma), streptomycin (100 μg/ml; Sigma), L-glutamine (2 mmol/liter; Sigma), and 10% autologous serum for 4 days. The cultures were then pulsed with 0.5 μCi of [^{3}H]thymidine for 4 hours. The cells were then harvested on filter paper discs, and the [^{3}H]thymidine uptake was determined by scintillation counting. The results were expressed as stimulation indices (ratio of counts with and without antigen) and as counts per minute for cultures stimulated with p27 (10 μg/ml); those stimulated with p27:Ty-VLP gave similar results. All cultures yielded high stimulation indices and counts with concanavalin A, and no significant counts were found with CTB or R20. The mucosal route of immunization did not elicit a rise in [^{3}H]thymidine uptake when the cells were stimulated with Ty-VLP. However, after IM administration of the immunogens, moderate responses were elicited by stimulation with Ty-VLP.
16. IgA antibodies to p27 and a control random peptide of 20 amino acids (R20) was determined by ELISA. Plates coated with antigen (at 1 μg/ml) were incubated with doubling dilutions of test samples. Bound antibody was detected by incubation with rabbit IgG to monkey IgA at 8 μg/ml or monkey IgG at 2 μg/ml (Nordic Immunological Laboratory), followed by affinity-purified goat antibody to rabbit IgG conjugated to alkaline phosphatase (Sigma Fine Chemicals) and *p*-nitrophenylphosphate disodium (Sigma Diagnostics). The reaction was terminated with 3 M NaOH, and the absorbance measured at a wavelength of 405 nm. Results are expressed as the reciprocal of the lowest dilution that gave an absorbance of 0.15 units above the background sample. The reproducibility of the ELISA after four repeated assays of the same vaginal fluid sample for IgA and IgG was within one dilution. The results with R20 were negative.
17. The construction of hybrid virus-like particles containing the SIV p27 sequence of isolate 32H of $SIVmac_{251}$ fused to the p1 protein of Ty has been described [N. R. Burns, J. E. M. Gilmour, S. M. Kingsman, A. J. Kingsman, S. E. Adams, *J. Mol. Biol.* **216**, 207 (1990); N. R. Burns, in *Methods in Molecular Biology*, M. Collins, Ed. (Humana, Clifton, NJ, 1991), vol. 8, p. 277]. The SIV gag p27 gene was derived from the clone pNIBSCI, and the p27:Ty-VLP and control Ty-VLP were purified from yeast extracts [N. Almond *et al.*, *J. Virol. Methods* **28**, 301 (1990)]. Nonparticulate p27 was prepared by cleavage from the p27:Ty-VLP and further purified by ion exchange chromatography. The absence of any Ty protein in the p27 preparation was confirmed by protein immunoblotting. The recombinant antigens were covalently linked to CTB (Sigma) at a ratio of 1:1 with SPDP (*N*-succinimidyl-3,2-pyridyl dithiopropionate) [C. Czerkinsky *et al.*, *Infect. Immun.* **57**, 1072 (1989)]. Six rhesus macaques received two oral, followed by three vaginal immunizations (O-V) of p27:Ty-VLP/CTB (n = 3), p27:Ty-VLP without CTB (n = 1), p27/CTB without Ty-VLP (n = 1), or p27 (n = 1) at monthly intervals. Three rhesus macaques and one cynomolgus macaque received two vaginal, followed by three oral (V-O) monthly immunizations of p27:Ty-VLP/CTB, and one control rhesus macaque received Ty-VLP/CTB. Topical vaginal administration of 200 μg of p27:Ty-VLP/CTB (or Ty-VLP/CTB) was carried out with soft, lubricated pediatric nasogastric tubes. Oral administration was performed by intragastric intubation of gelatin-coated capsules, containing 500 μg of the vaccine and 400 μl of cholera vibrio (Institut Merieux, Lyon, France) in the presence of sodium bicarbonate. One month after the last mucosal administration, all macaques were challenged by IM immunization with 200 μg of the preparation that we used to immunize that animal and mixed with aluminium hydroxide (AluGel, Uniscience, London, U.K.), except for the p27/CTB-immunized animal, which received 130 μg of p27/CTB in AluGel. Blood was collected from the femoral vessels, and the serum was separated. Vaginal and rectal washings were collected atraumatically with the aid of pediatric naso-gastric tubes that were flexible and lubricated. Samples were collected before and approximately 1 month after each immunization; the results shown are from samples taken approximately a month after the given immunization schedule. All procedures in the macaques were carried out after sedation with I M ketamine hydrochloride (10 mg/kg; Parke-Davis Veterinary).
18. We thank N. Graff and N. Burns (British Biotechnology, Ltd.) for preparing the SIV antigens and P. Kitchin and N. Almond (National Institute of Biological Standards and Control) for supplying plasmid pNIBSCI, containing the p27 gene we used to construct the p27:Ty-VLP. Supported by the Medical Research Council AIDS Directed Programme.

26 June 1992; accepted 21 September 1992

Encoding of a Homolog of the IFN-γ Receptor by Myxoma Virus

Chris Upton, Karen Mossman, Grant McFadden*

Many poxvirus-encoded virulence factors have been identified as proteins that are secreted from infected cells. The major secreted protein (37 kilodaltons) from cells infected with myxoma virus is encoded by the M-T7 open reading frame. This protein has significant sequence similarity to the human and mouse receptors for interferon-gamma (IFN-γ). Furthermore, the myxoma M-T7 protein specifically binds rabbit IFN-γ and inhibits the biological activity of extracellular IFN-γ, one of the key regulatory cytokines in the host immune response against viral infections.

The poxviruses comprise a family of large, complex, and relatively autonomous double-stranded DNA viruses that replicate in the cytoplasm of host eukaryotic cells (*1*). Although they have been shown to infect mammals, birds, reptiles, and insects, the severity of the disease produced by different poxviruses varies greatly (*2*, *3*). In general, poxvirus genomes are organized with essential genes clustered in the center, whereas virulence markers that govern pathogenesis tend to map toward the termini of the genome (*4*). A number of these virulence markers are secreted proteins that enhance the ability of the virus to propagate in its natural host but have only a minor effect, if any, in cultured cells. These "virokines" include epidermal growth factor–like growth factors, a complement binding protein, and serine protease inhibitors (*2*, *5*). Shope fibroma virus (SFV) encodes a secreted protein that has significant sequence similarity to the host tumor necrosis factor (TNF) receptor (*6*, *7*); the deletion of the homolog of this gene in the myxoma virus reduces the virulence of this virus considerably (*8*). Wild-type myxoma virus is extremely virulent in adult domestic rabbits and has apparently evolved multiple mechanisms to combat the host immune response to the infection (*9*). It therefore provides a useful model to study the general mechanisms of poxvirus virulence, a greater understanding of which is required for the development of safer poxvirus vaccines for humans and animals (*10*, *11*). The self-defense weapons that are encoded by such highly virulent viral pathogens (*12*) may also be important indicators of the relative value of the various components of the immune system in combating such disease agents in vivo.

Labeling studies have shown that a number of secreted proteins are specific to myxoma infected cells (*13*). Figure 1A shows proteins secreted at early and late (after viral DNA replication begins) times during an infection of BGMK cells by myxoma virus (strain Lausanne) in comparison to mock-infected cells. The most prominent [^{35}S]methionine + cysteine protein (arrow in Fig. 1A) was observed at both early (lane E) and late (lane L) times of infection. After concentration, the same protein was readily detected as the predominant band in Coomassie blue–stained polyacrylamide gels and migrated with an apparent size of ap-

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L15 ANSWER 4 OF 53 MEDLINE on STN
AN 1998117779 MEDLINE
DN PubMed ID: 9456663
TI Salivary and **mucosal immune** responses to **HIV** and its co-pathogens.
AU Challacombe S J; Sweet S P
CS Department of Oral Medicine and Pathology, UMDS Guy's Hospital, London, UK.
SO Oral diseases, **(1997 May)** 3 Suppl 1 S79-84. Ref: 38
Journal code: 9508565. ISSN: 1354-523X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Dental Journals; AIDS
EM 199802
ED Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980211
AB The profound effects that **HIV** induces in systemic **immunity** have been well characterised, but the situation with regard to **mucosal immune** responses is less clear. **Oral** cavity fluids have been used as a marker of the **mucosal immune** system. Whole and parotid saliva IgA, IgA1 and IgA2 concentrations have been found to be lower in both **HIV** infection and AIDS subjects, whereas serum IgA and IgA subclasses are markedly raised, suggesting a dichotomy between systemic and secretory immunity. Salivary antibodies to **HIV** can be readily detected and secretory IgA antibody can be neutralising to some strains of **HIV**. **HIV** vaccines can also induce antibody responses in saliva, but vaccination routes other than parenteral immunisation are needed. Antibody responses to **oral** microbes have also been studied and it has been shown that IgA, IgA1 and IgA2 subclass antibody titres to Candida albicans and to Streptococcus mutans are increased in whole or parotid saliva from **HIV** patients, but reduced in AIDS patients, suggesting a compensatory response which is overcome with progressive **immunodeficiency**. The avidity of salivary IgA antibodies to Candida in **HIV** seems unimpaired, whereas relative avidities of serum antibodies in **HIV** patients with candidiasis are lowered. Non-specific factors which may inhibit Candida and other opportunist pathogens are also found in saliva. The candidacidal, myelomonocytic protein calprotectin is present in saliva at levels which are biologically active, although levels are lowered in **HIV** infection. Overall, **HIV** infection appears to be associated with disregulation of a number of **immune** factors at the **mucosal** surface, but the ability of patients with **HIV** infection to mount specific antibody secretory responses seems to be relatively intact until late in infection.

L15 ANSWER 5 OF 53 MEDLINE on STN
AN 97454210 MEDLINE
DN PubMed ID: 9310285
TI Induction of **mucosal** and systemic responses against **human immunodeficiency virus** type 1 glycoprotein 120 in mice after **oral immunization** with a single dose of a Salmonella-**HIV** vector.
AU Wu S; Pascual D W; Lewis G K; Hone D M
CS Division of Infectious Diseases and Gastroenterology, School of Medicine, Johns Hopkins University, Baltimore, Maryland 21202, USA.

NC AI-32879 (NIAID)
AI-33230 (NIAID)
AI-38192 (NIAID)
+
SO AIDS research and human retroviruses, **(1997 Sep 20)** 13 (14) 1187-94.
Journal code: 8709376. ISSN: 0889-2229.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199710
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971028
AB Previous studies from our group showed that a Salmonella-**HIV** vector vaccine that expressed recombinant **HIV**-1 envelope protein gp120 stably in the vector cytoplasm elicited type 1 helper T cell (Th1) responses to gp120. Despite the promise of such vaccines, a major limitation in their use was that multiple immunizations were required to elicit even small responses. For this reason, we sought a modified vector configuration that would induce more potent gp120-specific T cell responses exhibiting a broader spectrum of effector functions after a single inoculation. In this article we describe the construction and immunogenicity of a Salmonella-**HIV** vector that displays a truncated derivative of **HIV**-1(IIIB) envelope in the periplasm of the vector. A single **oral** dose of this Salmonella vector, called H683(pW58-asd+), generated a gp120-specific proliferation response in the spleen 14 days after **immunization**. In agreement with our previous findings, the gp120-specific splenic CD4+ T cells elicited by H683(pW58-asd+) displayed a Th1 phenotype; however, gp120-specific splenic CD4+ Th2 cells were also evident. In addition, this strain induced strong gp120-specific IgA antibody-secreting cell (ASC) responses in the intestinal lamina propria and mesenteric lymph nodes. As many as 2% of the total lamina propria and mesenteric lymph node IgA ASCs were found to be specific for gp120 28 days after a single oral dose of H683(pW57-asd+). Because the proliferative response following a single dose of H683(pW58-asd+) was comparable to that seen previously after three doses of an analogous construct expressing recombinant gp120 in the cytoplasm, these observations suggest that Salmonella-vectored secreted **HIV**-1 antigens elicit higher T cell responses than their cytoplasmically bound analogs.

L15 ANSWER 8 OF 53 MEDLINE on STN
AN 97307610 MEDLINE
DN PubMed ID: 9164952
TI **Oral immunization** with simian **immunodeficiency** virus p55gag and cholera toxin elicits both **mucosal** IgA and systemic IgG **immune** responses in nonhuman **primates**.
AU Kubota M; Miller C J; Imaoka K; Kawabata S; Fujihashi K; McGhee J R; Kiyono H
CS The Immunobiology Vaccine Center, Department of Oral Biology, University of Alabama at Birmingham Medical Center, 35294, USA.
NC AI 35544 (NIAID)
AI35932 (NIAID)
DE 09837 (NIDCR)
+
SO Journal of immunology (Baltimore, Md. : 1950), **(1997 Jun 1)** 158 (11) 5321-9.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; AIDS
EM 199706
ED Entered STN: 19970630
Last Updated on STN: 20000303
Entered Medline: 19970619
AB Rhesus macaques were orally **immunized** with a **mucosal vaccine** consisting of two different concentrations (1 mg vs 250 microg) of recombinant SIV p55gag (p55) with or without cholera toxin (CT, 50 microg) as a **mucosal** adjuvant. The plasma from macaques receiving the higher dose of p55 (1 mg) and CT had higher p55-specific IgG and IgA Ab titers compared with macaques that received the lower dose of p55 (250 microg) and CT. Further, high levels of p55-specific IgG and IgA Abs were present in external secretions from both groups. The level of p55-induced T cell responses was elevated in PBMCs isolated from the high dose group compared with the low dose group. When culture supernatants from these p55-stimulated PBMCs were examined for Th1 (IFN-gamma) and Th2 (IL-4 and IL-10) cytokines, both IFN-gamma and IL-10 were present, but IL-4 was absent. CD4+ T cells isolated from these p55-stimulated PBMCs contained IFN-gamma spot-forming cells (SFCs) but not IL-4 SFCs. These results were further confirmed by cytokine-specific reverse transcriptase PCR analysis, where p55-specific CD4+ T cells expressed mRNA for IFN-gamma, IL-6, and IL-10, but not IL-4. These findings suggest that **oral immunization** of nonhuman **primates** induced both IFN-gamma-secreting Th1 and select Th2 cytokine (e.g., IL-6 and IL-10)-producing CD4+ Th cells, which accounted for the generation of p55-specific systemic and **mucosal** Ab responses.

L15 ANSWER 15 OF 53 MEDLINE on STN
AN 95038296 MEDLINE
DN PubMed ID: 7950860
TI Exploration of **mucosal immunity** in **humans**: relevance to **vaccine** development.
AU Czerkinsky C; Holmgren J
CS INSERM Unit 80, Hopital Edouard-Herriot, Lyon, France.
NC 3RO1HD26634-0151 (NICHD)
SO Cellular and molecular biology (Noisy-le-Grand, France), **(1994)** 40 Suppl 1 37-44. Ref: 21
Journal code: 9216789. ISSN: 0145-5680.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 199412
ED Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941229
AB Although the immune system is remarkably diverse, there is evidence that certain types of immune responses take place and are restricted to certain anatomic locations within the body. The concept of a common **mucosal immune** system that provides **immune** reactivity not only at the site of antigen deposition but also at remote **mucosal** sites may be explained by the utilization of organ-specific recognition molecules by circulating precursors of **mucosal immunoblasts** and by the production of certain maturation factors (e.g. cytokines, hormones) produced preferentially in certain organs or parts of a given organ. This notion may explain the unification of **immune** responses in diverse **mucosal**

sites and the physiologic segregation of **mucosal** from systemic **immune** mechanisms. Novel methods have been developed to enable studies of antigen specific B and T cell responses in various **mucosal** and extramucosal tissues in **primates** and rodents, using cholera toxin or its B subunit as prototype **immunogens** and **mucosal** carrier-delivery systems. The tissue localization and isotype commitment of antibody-secreting cells (ASC) and the homing potential of their circulating precursors have also been examined after **oral**, nasal, intra-tonsillar, rectal and/or genital **immunization**(s). The anatomical distribution of T- and accessory cell-derived cytokines has also been examined. These tools and approaches are being employed in studies attempting to induce optimal **mucosal immune** responses to several **mucosal** pathogens including **HIV**-1, in certain organs such as the lower gastrointestinal tract and the female urogenital tract.(ABSTRACT TRUNCATED AT 250 WORDS)

L15 ANSWER 17 OF 53 MEDLINE on STN
AN 93088063 MEDLINE
DN PubMed ID: 1360702
TI Induction of **mucosal** and systemic **immunity** to a recombinant simian **immunodeficiency** viral protein.
AU Lehner T; Bergmeier L A; Panagiotidi C; Tao L; Brookes R; Klavinskis L S; Walker P; Walker J; Ward R G; Hussain L; +
CS Division of Immunology, United Medical School, Guy's Hospital, London, United Kingdom.
SO Science, **(1992 Nov 20)** 258 (5086) 1365-9.
Journal code: 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199301
ED Entered STN: 19930129
Last Updated on STN: 19970203
Entered Medline: 19930107
AB Heterosexual transmission through the cervico-vaginal **mucosa** is the principal route of **human immunodeficiency virus** (**HIV**) infection in Africa and is increasing in the United States and Europe. Vaginal immunization with simian immunodeficiency virus (SIV) had not yet been studied in nonhuman **primates**. Immune responses in macaques were investigated by stimulation of the genital and gut-associated lymphoid tissue with a recombinant, particulate SIV antigen. Vaginal, followed by **oral**, administration of the **vaccine** elicited three types of **immunity**: (i) gag protein p27-specific, secretory **immunoglobulin** A (IgA) and **immunoglobulin** G (IgG) in the vaginal fluid, (ii) specific CD4+ T cell proliferation and helper function in B cell p27-specific IgA synthesis in the genital lymph nodes, and (iii) specific serum IgA and IgG, with CD4+ T cell proliferative and helper functions in the circulating blood.

L15 ANSWER 18 OF 53 MEDLINE on STN
AN 90264689 MEDLINE
DN PubMed ID: 2189002
TI In defense of **mucosal** surfaces. Development of novel **vaccines** for IgA responses protective at the portals of entry of microbial pathogens.
AU McGhee J R; Mestecky J
CS Department of Microbiology, University of Alabama, Birmingham.
NC AI 18958 (NIAID)

AI 19674 (NIAID)
DE 04217 (NIDCR)
+

SO Infectious disease clinics of North America, **(1990 Jun)** 4 (2) 315-41. Ref: 105
Journal code: 8804508. ISSN: 0891-5520.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)

LA English

FS Priority Journals

EM 199007

ED Entered STN: 19900810
Last Updated on STN: 20000303
Entered Medline: 19900703

AB A common **mucosal immune** system occurs in mammalian species, where antigen stimulation of BALT and GALT induces an exodus of specific lymphocytes that home to the various **mucosal** effector sites. These responses are finely regulated and T cells and cytokines are of central importance for ultimate plasma cell differentiation and for production of S-IgA antibodies in our external secretions. The current need for **vaccines**, including those to respiratory, gastrointestinal, and genitourinary tract infections as well as the universal efforts to develop **immunity** to **HIV** and AIDS, compels us to continue to better understand how we can use the common **mucosal immune** system to advantage for eventual prevention of infectious diseases. This article summarizes the various antigen delivery strategies and progress of **oral vaccines** for induction of protective **mucosal immune** responses to various viral and bacterial diseases.

L15 ANSWER 25 OF 53 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997:383816 CAPLUS

DN 127:70660

TI **Mucosal immunology** for the prevention of infectious diseases. The development of **mucosal vaccine**

AU Kubota, Mitsuru; Fujihashi, Kohtaro; Kiyono, Hiroshi

CS Vaccine Cent., Univ. Alabama, Birmingham, 35294-2170, USA

SO Kagaku to Seibutsu (**1997**), 35(6), 415-420
CODEN: KASEAA; ISSN: 0453-073X

PB Gakkai Shuppan Senta

DT Journal; General Review

LA Japanese

AB A review, with 21 refs., on characteristics of **mucosal immune** system, i.e. (1) production of antigen-specific secretory IgA (S-IgA) and (2) significance of CD4+ T cells in its regulation, use of cholera toxin (CT) and labile toxin of Escherichia coli as **mucosal** adjuvants for inducing **mucosal immunity**, and development of nasal influenza **vaccines** and **oral vaccines** for AIDS. **Immunol**. study on **oral** administration of p55 (gag protein of **HIV** virus) and CT adjuvant to rhesus **monkey** is also introduced.

L15 ANSWER 26 OF 53 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1996:541238 CAPLUS

DN 125:165692

TI Methods and compositions for inducing **mucosal immune** responses

IN Mitchell, William M.

PA Vanderbilt University, USA

SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9621356	A1	19960718	WO 1995-US8374	19950703 <--
	W: AU, CA, JP				
	US 6630455	B1	20031007	US 1995-372429	19950113
	CA 2209064	AA	19960718	CA 1995-2209064	19950703 <--
	AU 9529587	A1	19960731	AU 1995-29587	19950703 <--
	AU 700519	B2	19990107		
PRAI	US 1995-372429	A	19950113		
	WO 1995-US8374	W	19950703		

AB The invention provides a method of inducing a **mucosal immune** response in a subject, comprising administering to the **mucosa** of the subject an amount of antigen-encoding DNA effective to induce a **mucosal immune** response complexed to a transfection-facilitating lipospermine or lipospermidine. In the method of inducing a **mucosal immune** response, the antigen-encoding DNA can encode an antigen that is expressed on the surface of infected cells during the course of infection. DNA encoding the envelope glycoproteins of viral pathogens is used in the present method. Lipospermines and lipospermidines are bifunctional mols. consisting of one or more hydrophobic chains covalently linked to a cationic grouping in which there is coordination of three or more amide hydrogens with a phosphate oxygen of the DNA chain forming an ionic charge complex. One preferred example of a lipospermine is DOGS (dioctadecylamidoglycylspermine). The invention also provides a composition, comprising an amount of DNA encoding an envelope antigen or envelope-associated antigen of a pathogen complexed to a lipospermine. More specifically, the invention provides a composition, comprising an amount of DNA encoding an envelope antigen of **HIV** complexed to a lipospermine.

L15 ANSWER 28 OF 53 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:245763 CAPLUS
DN 125:7588
TI Induction of **mucosal immunity** against **HIV**
AU Bukawa, Hiroki; Fujita, Kiyohide; Okuda, Kenji
CS Sch. Med., Yokohama City Univ., Yokohama, 236, Japan
SO Saishin Igaku (**1996**), 51(4), 492-8
CODEN: SAIGAK; ISSN: 0370-8241
DT Journal; General Review
LA Japanese
AB A review with 21 refs., on **oral immune** tolerance and induction of **mucosal immunity**, induction of **mucosal immunity** to simian **immunodeficiency** virus, and neutralization of **HIV** by **mucosal** secretory **HIV**-specific IgA antibody induced by a synthetic peptide **vaccine** candidate.

L15 ANSWER 32 OF 53 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 1995:290998 BIOSIS
DN PREV199598305298
TI **Oral immunization** of mice with a live attenuated Salmonella vector expressing recombinant gp120 of **HIV**-1 on the surface of the vector, induces **mucosal** and systemic **immunity** against gp120.
AU Powell, Robert J. [Reprint author]; Wu, Shaoguang [Reprint author];

Pascual, David W.; Van Cott, John; McGhee, Jerry; Lewis, George K. [Reprint author]; Hone, David M. [Reprint author]
CS Univ. MD, Baltimore, MD, USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (1995) Vol. 95, No. 0, pp. 294.
Meeting Info.: 95th General Meeting of the American Society for Microbiology. Washington, D.C., USA. May 21-25, 1995.
ISSN: 1060-2011.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 5 Jul 1995
Last Updated on STN: 5 Jul 1995

L15 ANSWER 36 OF 53 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 1994:11099 BIOSIS
DN PREV199497024099
TI **Mucosal vaccine** for AIDS: **Oral immunization** with **HIV** gp120 in combination with liposome and cholera toxin induces antigen-specific IgA producing cells.
AU Merrill, K. W. [Reprint author]; Pietrobon, P. J. Freda; Fujihashi, K.; McGhee, J. R.; Kiyono, H.
CS Immunobiology Vaccine Cent., Dep. Oral Biology, Univ. Ala. Birmingham, Birmingham, AL 35294, USA
SO AIDS Research and Human Retroviruses, (1993) Vol. 9, No. SUPPL. 1, pp. S36.
Meeting Info.: Fifth Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS on Advances in AIDS Vaccine Development. Chantilly, Virginia, USA. August 30-September 3, 1992.
CODEN: ARHRE7. ISSN: 0889-2229.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 23 Jan 1994
Last Updated on STN: 23 Jan 1994

L15 ANSWER 40 OF 53 EMBASE
on STN
AN 1998152165 EMBASE
TI Induction of protective **mucosal** antibodies, T cells, and β chemokines.
AU Lehner T.; Wang Y.; Cranage M.; Bergmeier L.A.; Mitchell E.; Kelly C.G.; Tao L.; Hall G.; Dennis M.; Cook N.; Klavinskis L.; Jones I.; Ward R.
CS T. Lehner, Department of Immunology, United Medical and Dental School, Guy's Hospital, London SE1 9RT, United Kingdom
SO AIDS Research and Human Retroviruses, (1998) 14/SUPPL. 1 (S77-S78).
ISSN: 0889-2229 CODEN: ARHRE7
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB **Mucosal** transmission of **HIV** is responsible for the rectal, vaginal, male genital, and possibly **oral** routes of infection. With the identification of coreceptors in **HIV**/SIV binding and fusion a new approach has been opened in **HIV**/SIV transmission and protection. **Mucosally** targeted vaccination aims to elicit secretory IgA and IgG antibodies at the **mucosal** surface and CD4+ and CD8+ T cell functions in the **mucosal**

tissues, the draining lilac lymph nodes, and the circulating blood. In addition, however, β chemokines may be induced, especially by stimulating CD8 cells, and these inhibit **HIV**/SIV replication by blocking CCR-5 receptors expressed on the surface of CD4+ T cells. **Immunization** of macaques by targeting the rectal **mucosa** draining iliac lymph nodes (TLN) with SIV gp120 and p27 antigens was followed by rectal challenge with the SIVmac 32H J5 molecular clone. Total protection was induced in 4 of 7 macaques, compared with infection in 13 of 14 macaques unimmunized or **immunized** by other routes ($p = 0.025$). The remaining three macaques showed a decrease in viral load (>90%), indicating that all seven TLN-**immunized** macaques showed total or partial protection ($p = 0.001$). Protection was associated with an increase in the iliac lymph nodes of IgA antibody-secreting cells to p27 ($p < 0.02$), rectal, urinary, and serum IgA and IgG antibodies, and T cell-proliferative responses to gp120 and p27. However, the most significant association was found between protection and CD8-suppressor factor ($p < 0.01$), the β chemokines RANTES ($p < 0.01$), MIP- 1β ($p < 0.01$), and possibly MIP-1α in the lilac lymph nodes. The coreceptor CC-R5 is also found in simian CD4+ T cells and SIV replication in these cells can be inhibited by the β chemokines. **Immunization** against **mucosal** transmission of SIV/**HIV** can not be broadened to elicit, in addition to sIgA and IgG and cytotoxic CD8 cells, CD8-SF and the integral chemokines in the **mucosal** tissues and the inductive lilac lymph nodes.

L15 ANSWER 44 OF 53 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 92329412 EMBASE
DN 1992329412
TI **Mucosal** approaches to **HIV vaccine** development.
AU Forrest B.D.
CS Division of Communicable Diseases, Department of Medical Microbiology, Royal Free Hospital Sch. of Medicine, Rowland Hill Street,London NW3 2QG, United Kingdom
SO AIDS Research and Human Retroviruses, (1992) 8/8 (1523-1525). ISSN: 0889-2229 CODEN: ARHRE7
CY United States
DT Journal; Conference Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English

L15 ANSWER 45 OF 53 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 97:538896 SCISEARCH
GA The Genuine Article (R) Number: XK471
TI Intranasal **immunization** is superior to vaginal, gastric, or rectal **immunization** for the induction of systemic and **mucosal** anti-**HIV** antibody responses
AU Staats H F (Reprint); Montgomery S P; Palker T J
CS DUKE UNIV, MED CTR, DEPT MED, BOX 3307, DURHAM, NC 27710 (Reprint); DUKE UNIV, MED CTR, DEPT IMMUNOL, DURHAM, NC 27710; DUKE UNIV, MED CTR, CTR AIDS RES, DURHAM, NC 27710
CYA USA
SO AIDS RESEARCH AND HUMAN RETROVIRUSES, (**20 JUL 1997**) Vol. 13, No. 11, pp. 945-952.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538.

ISSN: 0889-2229.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 40
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Vaginal anti-**HIV** antibody responses may be beneficial, and possibly required, for **vaccine**-induced protection against **HIV** infection acquired through receptive vaginal intercourse, We have previously determined that intranasal **immunization** with a hybrid **HIV** peptide and cholera toxin induced vaginal anti-**HIV** IgA responses in BALB/c and C57BL/6 mice, To determine if vaginal, gastric, or rectal boosting would enhance the induction of vaginal anti-**HIV** IgA responses over those observed with intranasal **immunization** only, C57BL/6 mice were intranasally **immunized** with the hybrid **HIV** peptide T1SP10MN(A) and cholera toxin (days 0 and 14) and boosted,ia the vaginal, gastric, or rectal route (days 7 and 28), Four intranasal **immunizations** was superior to all other **immunizations** evaluated for the induction of plasma anti-peptide IgG, vaginal anti-peptide IgG and IgA, and peptide-specific delayed-type hypersensitivity. In addition, intranasal priming with gastric boosting was associated with greatly elevated total serum IgE concentrations whereas intranasal **immunization** only was associated with only a modest increase in total serum IgE, These results suggest that intranasal **immunization** is a viable route of **immunization** for the induction of systemic and **mucosal** anti-**HIV immune** responses.

L15 ANSWER 46 OF 53 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 97:529741 SCISEARCH
GA The Genuine Article (R) Number: XJ336
TI **Mucosal immunization** with a DNA **vaccine** induces **immune** responses against **HIV**-1 at a **mucosal** site
AU Wang B (Reprint); Dang K; Agadjanyan M G; Srikantan V; Li F; Ugen K E; Boyer J; Merva M; Williams W V; Weiner D B
CS UNIV PENN, SCH MED, DEPT PATHOL & LAB MED, PHILADELPHIA, PA 19104 (Reprint); UNIV PENN, SCH MED, DEPT MED, DIV RHEUMATOL, PHILADELPHIA, PA 19104; UNIV PENN, SCH MED, INST BIOTECHNOL & ADV MOL MED, PHILADELPHIA, PA 19104; UNIFORMED SERV UNIV HLTH SCI, DEPT SURG, BETHESDA, MD 20814; UNIV S FLORIDA, COLL MED, DEPT MED MICROBIOL & IMMUNOL, TAMPA, FL 33612
CYA USA
SO VACCINE, (**JUN 1997**) Vol. 15, No. 8, pp. 821-825.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, OXON, ENGLAND OX5 1GB.
ISSN: 0264-410X.
DT Article; Journal
FS LIFE; AGRI
LA English
REC Reference Count: 14
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB **Mucosal immunity** is the first defense system in protection against **mucosal** infection by sexually transmitted diseases and subsequent systemic dissemination of infection. Development of **vaccines** which can induce protective **mucosal immunity** would have great promise for preventing sexually transmitted diseases including AIDS, DNA **vaccines** have recently shown certain advantages over other types of **vaccines** in safety and elicitation of specific **immune** responses. We have hypothesized that direct delivery of a DNA plasmid coding the **HIV**

-1 envelope (pcMN160) via **mucosal** routes will stimulate **mucosal immunity** against **HIV**-1. The expression of DNA plasmid inoculated intravaginally was detected in various tissues. Intravaginal inoculation of pcMN160 elicits production of vaginal **immunoglobulins** which specifically bind to the **HIV**-I envelope and neutralize **HIV**-I infectivity in vitro. These results indicate the feasibility of inducing **mucosal immunity** following **mucosal** inoculation of DNA **vaccines**. When coupled with systemic inoculation of appropriate DNA constructs, effective **mucosal** and systemic **immunity** may be generated. (C) 1997 Elsevier Science Ltd.

L15 ANSWER 48 OF 53 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 95:835799 SCISEARCH
GA The Genuine Article (R) Number: TH090
TI THE CELLS OF **ORAL-MUCOSA IMMUNE**-SYSTEM UPON **HIV**-INFECTION
AU PIMPINELLI N (Reprint); FICARRA G; ROMAGNOLI P
CS UNIV FLORENCE, INST ODONTOGNATHO STOMATOL, DERMATOL CLIN 2, FLORENCE, ITALY; UNIV FLORENCE, DEPT HUMAN ANAT & HISTOL, FLORENCE, ITALY
CYA ITALY
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (**DEC 1995**) Vol. 105, No. 6, pp. 60.
ISSN: 0022-202X.
DT Conference; Journal
FS LIFE; CLIN
LA ENGLISH
REC No References

L15 ANSWER 51 OF 53 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 94:745600 SCISEARCH
GA The Genuine Article (R) Number: PT118
TI **MUCOSAL IMMUNITY** IN THE FEMALE GENITAL-TRACT - RELEVANCE TO VACCINATION EFFORTS AGAINST THE **HUMAN-IMMUNODEFICIENCY-VIRUS**
AU MESTECKY J (Reprint); KUTTEH W H; JACKSON S
CS UNIV ALABAMA, DEPT MICROBIOL & MED, DEPT MICROBIOL BBRB 757, 845 19TH ST S, BIRMINGHAM, AL, 35294 (Reprint); UNIV TEXAS, SW MED CTR, DEPT OBSTET & GYNECOL, DALLAS, TX, 75235; UNIV ALABAMA, DEPT MICROBIOL, BIRMINGHAM, AL, 35294
CYA USA
SO AIDS RESEARCH AND HUMAN RETROVIRUSES, (**1994**) Vol. 10, Supp. 2, pp. S11-S20.
ISSN: 0889-2229.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 54
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The development of **vaccines** that induce specific **immune** responses in the genital tract secretions would have far-reaching implications for the prevention of AIDS and other sexually transmitted diseases. Most of the currently studied **vaccines** utilize systemic routes of **immunization** that are of limited value for the prevention of **mucosa**-contracted diseases. The relative contribution of antigen-sensitized cells and IgA-committed lymphocytes from IgA inductive sites (e.g., Peyer's patches and rectal tonsils) to remote or adjacent effector sites (e.g., salivary glands and female genital tract) as manifested by the appearance of corresponding

secretory antibodies has not been studied in **humans** despite its unquestionable practical importance. Exploitation of **immunization** routes that are effective for induction of **mucosal immune** responses and reflect our current knowledge of the origin of antibodies and of specific antibody-forming cells in **mucosal** tissues is likely to reduce the incidence of many infectious diseases including AIDS.